European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14

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Abstract

Background Contact allergy is a common condition and can severely interfere with daily life or professional activities. Due to changes in exposures, such as introduction of new substances, new products or formulations and regulatory intervention, the spectrum of contact sensitization changes.

Objective To evaluate the current spectrum of contact allergy to allergens present in the European baseline series (EBS) across Europe.

Methods Retrospective analysis of data collected by the European Surveillance System on Contact Allergies (ESSCA, www.essca-dc.org) in consecutively patch-tested patients, 2013/14, in 46 departments in 12 European countries.

Results Altogether, 31 689 patients were included in the analysis. Compared to a similar analysis in 2004, the prevalence of contact allergy to methylisothiazolinone went up to around 20% in several departments. In comparison, contact allergy to the metals nickel, cobalt and chromium remained largely stable, at 18.1%, 5.9% and 3.2%, respectively, similar to mostly unchanged prevalence with fragrance mix I, II and *Myroxylon pereirae* (balsam of Peru) at 7.3%, 3.8% and 5.3%, respectively. In the subgroup of departments diagnosing (mainly) patients with occupational contact dermatitis, the prevalence of work-related contact allergies such as epoxy resin or rubber additives was found to be increased, compared to general dermatology departments.

Conclusion Continuous surveillance of contact allergy based on network data offers the identification of time trends or persisting problems, and thus enables focussing in-depth research (subgroup analyses, exposure analysis) on areas where it is needed.

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Conflicts of interest

V.M. has received lecturing fees from Smart Practice Germany for scientific talks on unrelated topics. R.S. is shareholder and scientific adviser of the Polish representative of Chemotechnique Diagnostics. W.U. accepted travel reimbursement and partly honorarium for presentations given to cosmetic industry (associations) by them and received a lecture fee from Almirall Hermal for educational lectures on contact allergy. M.W. attended a drug advisory board meeting for GlaxoSmithKline (alitretinoin). The other authors do not declare a conflict of interest pertinent to this study.

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Introduction

Contact sensitization (CS) in terms of a delayed-type hypersensitivity can be directed to a multitude of low molecular weight substances, i.e. natural or synthetic haptens. Sensitization is diagnosed by patch testing, for which standards have recently been published by the European Society of Contact Dermatitis (ESCD).[1] The frequency of CS has been examined in a population-based study in five European countries conducted between 2008 and 2011. In this study, 27.0% of the representative patch-tested sample (n = 3119) had at least one positive reaction to an allergen of the European baseline series (EBS).[2] As population-based epidemiological studies are valuable, but infrequently performed, continuous epidemiological surveillance of CS relies on clinical networks collecting routine patch test data. The aim is to provide a timely public health alert concerning increasing trends or persisting problems, or a feedback regarding the success of preventive action, as indicated.

As one such network, the European Surveillance System on Contact Allergies (ESSCA, www.essca-dc.org, last accessed on 14 February 2017), which has been operative since 2002, presently links departments of dermatology in 12 European countries and collects data from about 15 000 patients per year. Several analyses of patch test results with the EBS in patients patch-tested for suspected CS in the participating departments have been published since 2002, e.g. Hegewald *et al.*[3], lately also including more in-depth views on different groups of allergens from the EBS, such as fragrances,[4] metals,[5] preservatives,[6] rubber chemicals[7,8] or topical therapeutics and excipients.[9] Following the main approach of providing a concise overview of the full range of EBS allergens as in Hegewald *et al.*[3] we herewith present an update of the data collection period 2013/14. To enable easier comparisons with previous results obtained in 2004, published in this journal,[3] we follow a largely similar presentation.

Methods

The retrospective analysis is based on routine clinical data collected by the ESSCA network, which has already been described in previous publications.[3] Briefly, clinical and demographic data, along with patch test results, of all patients patch-tested in the departments participating in ESSCA for suspected allergic contact dermatitis due to various potential exposures are documented electronically in the local departments. These use diverse data capture software and partly the multilingual software WinAlldat/ESSCA provided by ESSCA.[10] Standardized patch testing follows international recommendations.[1] The anonymized data delivered by the participants are pooled in the ESSCA data centre in Erlangen for further analysis,[11] using R (version 3.2.3) software (www.r-project.org, last accessed on 14

February 2017). Considering the fact that all individual identifiers were removed from the collected data, and no quasi-unique profiles, but only aggregated results are reported, such pooled analysis is deemed compliant with data protection requirements. Pertinent guidelines for the statistical analysis of patch test data[12,13] were considered. The maximum patch test reaction between day 3 and day 5 (inclusive) was aggregated as patch test outcome. Reactions designated as either +, ++ or +++ were classified as positive (allergic), and the remainder as non-allergic. The study period was 01/2013 to 12/2014, including 12 European countries and, in total, 46 departments.

Test results with the EBS valid in the study period, during which methylisothiazolinone (MI) 2000 ppm aq. had been added, and the recommended test concentration of methylchloroisothiazolinone (MCI)/MI had been increased from 100 to 200 ppm, and of formaldehyde from 1% to 2%,[14] were analysed. Altogether, 31 689 patients have been registered who were tested with the EBS and were read at least between day (D) 3 and D5. The TRUE Test® employing a hydrocellulose matrix for the haptens instead of petrolatum or water had been used in a relatively small number of patients, namely $n = 1214$, while the vast majority of patients was tested with petrolatum- and water-based haptens and investigator-loaded chambers systems, respectively. Moreover, two German departments use a 1-day patch test exposure, applied to $n = 948$ patients. Because in previous analyses, the impact of these variations in standard technique has been found to be limited, except for, e.g., fragrance mix I as tested with the TRUE Test®,[15] the results have all been pooled, but were annotated in case extreme values were observed related to one of these factors.

Results

In the years 2013 and 2014, altogether 31 689 patients have been patch-tested in the 46 European departments. The three departments contributing the lowest number of patients were SI-07 ($n = 49$), ES-05 ($n = 121$) and ES-06 ($n = 129$). On the other end, the three departments contributing the largest number of patients were NL-02 ($n = 2019$), DK-01 ($n = 2139$) and UK-99 ($n = 2503$). A wide variation in the proportion of male patients and patients aged 40 or above can be observed between departments and also between countries, as shown in Fig. 1a,b. For instance, the average age of patients patch-tested in German department is higher than in UK departments. Table 1 provides an overview of the characteristics of the patients of the participating departments according to the MOAHLFAP index.[16] For this purpose, specialized departments were grouped, and analysis stratified for (i) general dermatology departments ($n = 39$), (ii) occupational departments ($n = 6$, including the FIOH, Helsinki, FI, Osnabrück and Heidelberg, DE, Trieste, IT, Łodz, PL, and Cádiz, ES) and (iii) the one purely paediatric department in Padova, IT. The patient characteristics show considerable variation, also within the two subgroups of general and occupational

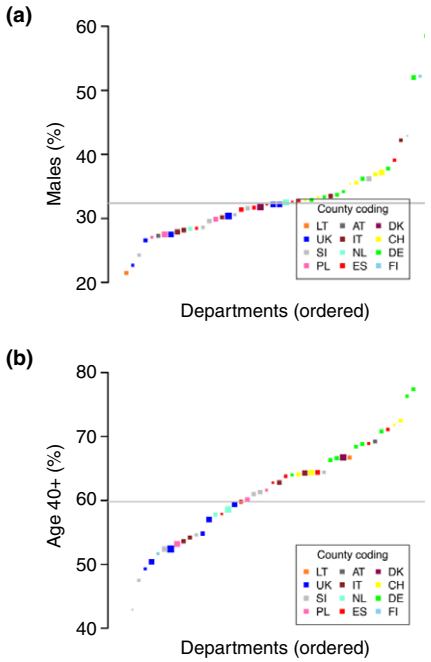

Figure 1 Departmental and national variation in the percentage of male patients (a) and of patients aged 40 and above (b).

departments, with a characteristic predominance of male, occupational and hand dermatitis patients in the latter subgroup. As an extension of the MOAHLFAP index, the proportion of patients with dermatitis of the trunk and generalized dermatitis, respectively, have been analysed, revealing a large variation between departments and, moreover, a considerable overall proportion of these patterns of dermatitis.

Patch test results with the EBS in the 39 general dermatology departments are shown in Table 2, together with the results of the one paediatric dermatology department in Padova, Italy. Overall crude and standardized results, as well as minimum and maximum standardized prevalence are presented. This follows the approach in Fehler[3], also by using the same ranking by decreasing standardized sensitization prevalence. Where applicable, results are stratified for different test concentrations as partly used. The considerable variation between departments, partly also within one country, is reflected by the fact that all allergens of the EBS elicited some positive reactions in some departments, while in other departments, they have been entirely negative.

Concerning the six departments specialized in occupational dermatology, the results with the EBS are shown in Table 3. Comparing the sensitization prevalence to EBS allergens between these departments, variation related to differing age- and sex-structure (Table 1) should largely have been eliminated by using age- and sex-standardized[17] prevalence, as in the general

Table 1 Characteristics of (patients of) the departments participating in the ESSCA network 2013/14, including the MOAHLFAP index,[16] stratified for non-specialized departments ($n = 39$), occupational dermatology departments ($n = 6$) and the paediatric dermatology department in Padova, Italy. The 'Avg. %' column indicates the average of the respective group

		Non-specialized			Occupational			Paediatric
		Avg. %	min. %	max. %	Avg. %	min. %	max. %	%
Male	M	31.3	21.5 (Kaunas, LT)	42.9 (Ljubljana/Clinic, SI)	43.3	27.1 (Łodz, PL)	58.5 (Heidelberg, DE)	42.2
Occupational dermatitis	O	10.3	1.3 (Middlesbrough, UK)	43.4 (León, ES)	44.6	11.2 (Trieste, IT)	76.8 (Osnabrück, DE)	0
Atopic dermatitis	A	23.3	8.8 (León, ES)	44.3 (Oxford, UK)	28.1	8.3 (Trieste, IT)	54.2 (Osnabrück, DE)	55.9
Hand dermatitis	H	21	9.1 (Napoli, IT)	42.5 (Vigo, ES)	61.6	24.2 (Trieste, IT)	89.2 (Osnabrück, DE)	16.4
Leg dermatitis	L	4.1	1.3 (Napoli, IT)	14.8 (Dresden, DE)	2.0	0.6 (Osnabrück, Heidelberg, DE)	3.9 (Trieste, IT)	11.3
Face dermatitis	F	17	3 (Napoli, IT)	37.6 (Oxford, UK)	6.3	1.5 (Heidelberg, DE)	17.2 (Łodz, PL)	19.3
Age 40+	A	60.2	42.9 (Ljubljana/Clinic, SI)	77.4 (Kiel, DE)	63.8	51.7 (Helsinki, FI)	68.8 (Heidelberg, DE)	0
At least 1 positive reaction	P	44.1	29.9 (Celje, SI)	60.5 (León, ES)	41.1	32.2 (Osnabrück, DE)	53.7 (Łodz, PL)	21.9
Trunk dermatitis		7.4	0 (Krakow, PL)	37.9 (Barcelona/IMAS, ES)	3.1	0.3 (Osnabrück, DE)	8.4 (Łodz, PL)	9.0
Generalized dermatitis		9.1	0 (León, Krakow)	26.3 (London, UK)	7.8	2.0 (Osnabrück, DE)	18.5 (Heidelberg, DE)	7.1

For the 'OAHL' characteristics, data were not recorded in the Slovenian departments. The 'P' percentage refers to positive reactions only to allergens of the EBS, not to possible departmental or national extensions thereof.
Avg., average; min, minimum; max, maximum.

comparison. Hence, differences in the relative frequency of contact allergies are most likely due to other factors, partly reflected by the other MOAHLFAP factors (Table 1) as well as presumably unmeasured effects (see discussion).

Discussion

The present analysis addresses the current spectrum of contact allergy across 12 European countries, represented by a range of 1–8 departments, 10 years after a previous analysis published in the *JEADV*. The scope of participating countries has remained constant, with the addition of Slovenia since 2009, and limited changes of departments participating in ESSCA were in effect (e.g. St. John's, London, joining and several UK departments involuntarily dropping out due to software problems). Therefore, a comparison between the two sampling periods is an interesting option for discussing results.

First, the patient population characteristics, which are strongly associated with the spectrum of contact allergy found in a department,[17] are of interest. The MOAHLFAP index, recently expanded by additionally considering the percentage of patients positive to at least one baseline series allergen,[16] has proven useful for a basic description of the patients patch-tested in a certain department, or other defined subgroups. Compared to the earlier period (2004), a slight decrease in the percentage of male patients and particularly in the percentage of patients with occupational dermatitis is noted in the 'general' dermatology departments. In contrast, the proportion of patients with atopic dermatitis (in the UK traditionally comprising atopic patients in general) has increased considerably, although the age-structure has shifted towards older age – with marked differences (Fig. 1b). It can only be speculated whether such increase is a true reflection of an increase in atopic diseases, including atopic eczema, or merely related to the slight changes in contributing departments. Interesting, but difficult to explain, is a considerable decrease in the percentage of hand and leg dermatitis, while the percentage of patients with face dermatitis remained largely constant, possibly driven by the epidemic of MI contact allergy[18] often affecting the face due to cosmetic exposures.[19] At least the decrease in contact allergy to topical drugs (and thus, e.g., of leg dermatitis) is consistent with findings from other departments.[20] Interdepartmental differences in the percentage of patients with at least one positive reaction to the (European) baseline series have been noted throughout all ESSCA analyses, including Hegewald *et al.*[3] In this analysis, we restricted the set of baseline series allergens to those present in the EBS[14] to increase comparability. Due to the fact that some national groups and departments, respectively, choose to omit certain allergens of the EBS in their baseline series recommendations, the overall yield in these departments will evidently be somewhat lower; further aspects, also including differing selection processes, health systems and methodological issues, have been analysed and discussed in detail in Uter *et al.*[21] Focussing on the departments

Table 2 Patch test results with the European baseline series valid during the study period,[14] with, however, partly diverging patch test concentrations, obtained in non-specialized ESSCA departments. At the very right, results in the Padova department of paediatric dermatology as crude % positives (=374 to 376). The maximum reading between day (D)3 and D5 (inclusive) was considered. stand., standardized for age and sex[17]; allergens in decreasing order of standardized prevalence. nr (test), number of patients tested (in all general and the one paediatric department)

	Conc. %	nr (test)	Crude % positives	Stand. % positives	95% CI	Minimum % positives	Maximum % positives	Paediatric department crude %
Nickel sulphate	5	28 109	18.7	18.1	17.7–18.6	7.6 (4–11.3) Dortmund (DE)	35.3 (29.2–41.3) León (ES)[TT]	9.1 (6.4–12.5)
Methylisothiazolinone*	0.02	4383	10.7	10.2	9.3–11.1	6.9 (5.7–8.1) Krakow (PL)	19.6 (15–24.3) Madrid/Princesa (ES)	–
Methylisothiazolinone*	0.05	6713	7.4	7.3	6.6–7.9	0.6 (0–1.5) Graz (AT)	19.9 (9.8–29.9) Murcia (ES)	–
Methylisothiazolinone*	0.2	6677	7.8	7.6	6.9–8.2	6.4 (5.1–7.8) Newport (UK)	20.8 (10.7–30.9) Murcia (ES)	–
Fragrance mix I	8	27 892	7.8	7.3	7–7.6	0 (0–2.5) Aarau (CH)	16 (12.3–19.7) Kiel (DE)[D1]	0 (0–1)
MCI/MI*	0.01	19 790	7.4	7.3	6.9–7.7	1 (0.3–1.7) Celje (SI)	17.9 (13.4–22.3) Madrid/Princesa (ES)[TT]	1.9 (0.8–3.8)
MCI/MI*	0.02	9722	7.7	7.3	6.8–7.9	3.5 (2.7–4.3) Copenhagen (DK)	15.8 (11.4–20.1) Alicante (ES)	–
Cobalt chloride	1	27 873	5.9	5.9	5.6–6.2	0 (0–45.1) Napoli (IT)	13.8 (11.5–16) Poznan (PL)	8.8 (6.1–12.1)
Myroxylon pereirae (balsam of Peru)	25	27 274	5.7	5.3	5–5.6	0.7 (0–1.7) León (ES)[TT]	13.3 (10.3–16.4) Graz (AT)	0.5 (0.1–1.9)
Fragrance mix II	14	28 145	4	3.8	3.6–4	0.4 (0–1.1) Middlesbrough (UK)	9.1 (5.3–12.9) Göttingen (DE)	–
Potassium dichromate	0.5	26 390	3.3	3.2	3–3.4	0 (0–2.5) Aarau (CH)	11.4 (9.3–13.6) Poznan (PL)	4.5 (2.7–7.1)
p-Phenylenediamine	1	24 931	3.3	3.2	3–3.4	1.4 (0.3–2.4) Vigo (ES)	6.1 (4.3–7.8) Napoli (IT)	0 (0–1)
Colophonium	20	26 991	2.9	2.8	2.6–3	0.3 (0–0.6) Genova (IT)	5.2 (2.9–7.6) Kiel (DE)[D1]	0 (0–1)
MDBGN	0.2	5498	2.5	2.2	1.8–2.6	1.4 (0–3) Dortmund (DE)	3.7 (0.9–6.6) Aarau (CH)	–
MDBGN	0.3	13 831	2	1.9	1.6–2.1	0 (0–1.3) Middlesbrough (UK)	6.1 (5.1–7.1) Amsterdam VU (NL)	–
MDBGN	0.5	8246	2.4	2.2	1.9–2.5	0.4 (0–1.2) León (ES)[TT]	7.5 (0.2–14.7) Ljubljana/Clinic (SI)	–
Lanolin alcohol	30	26 178	1.9	1.9	1.7–2.1	0 (several departments)	6.5 (4–8.9) Erlangen (DE)	0.5 (0.1–1.9)
Thiuram mix	1	28 610	2	1.9	1.8–2.1	0.4 (0–1.2) León (ES)[TT]	4.5 (2.5–6.5) Erlangen (DE)	–
HICC	5	27 225	1.7	1.7	1.5–1.8	0.4 (0–1.1) Middlesbrough (UK)	4.7 (1.8–7.5) Göttingen (DE)	–
Formaldehyde*	1	19 829	1.5	1.5	1.4–1.7	0 (0–1) Alicante (ES)	3.5 (0.6–6.4) León (ES)[TT]	0 (0–1)
Formaldehyde*	2	9972	1.8	1.7	1.4–1.9	0 (0–1) Alicante (ES)	2.6 (2–3.2) London (UK)	–
Neomycin sulphate	20	23 385	1.3	1.2	1.1–1.4	0 (several departments)	10.9 (0–26.2) Kiel (DE)[D1]	1.6 (0.6–3.4)
Epoxy resin	1	28 577	1.1	1.1	1–1.2	0 (several departments)	4.9 (0.2–9.5) Aarau (CH)	0 (0–1)
Tixocortol pivalate	0.1	14 130	0.5	0.5	0.4–0.6	0 (several departments)	1 (0.4–1.7) Poznan (PL)	0.3 (0–1.5)
Tixocortol pivalate	1	8517	0.9	0.9	0.7–1.1	0 (0–0.6) Basel (CH)	1.4 (0.9–2) Amsterdam VU (NL)	–
Quaternium 15	1	18 404	0.8	0.8	0.7–0.9	0 (several departments)	2.9 (0.1–5.7) León (ES)[TT]	0.8 (0.2–2.3)
Budesonide	0.01	12 863	0.8	0.8	0.6–0.9	0 (several departments)	2.4 (1.3–3.5) Poznan (PL)	0 (0–1)
Budesonide	0.1	9009	0.4	0.3	0.2–0.5	0 (several departments)	1 (0.3–1.7) Basel (CH)	–
Mercapto mix (CBS, MBTS, MOR)	1	9978	0.7	0.7	0.5–0.9	0.2 (0–0.5) Dresden (DE)[D1]	1.9 (0.4–3.4) Jena (DE)	–
Mercapto mix (MBT, CBS, MBTS, MOR)	2	17 664	0.7	0.7	0.6–0.8	0 (several departments)	2.1 (0–5) Murcia (ES)[TT]	–
Mercaptobenzothiazole	2	28 618	0.6	0.6	0.5–0.7	0 (several departments)	2.7 (0–5.8) Murcia (ES)[TT]	0.3 (0–1.5)
Sesquiterpenlactone mix	0.1	13 405	0.8	0.7	0.6–0.9	0 (several departments)	1.2 (0.3–2.2) Cardiff (UK)	–
ptBFR	1	24 743	0.7	0.7	0.6–0.8	0 (several departments)	2.2 (1.1–3.3) Groningen (NL)[TT]	0 (0–1)
Benzocaine	5	13 085	0.6	0.6	0.5–0.7	0 (several departments)	1.8 (0.6–3.1) Vigo (ES)	0 (0–1)
IPPD	0.1	24 163	0.6	0.6	0.5–0.7	0 (several departments)	1.8 (0.5–3) Erlangen (DE)	0 (0–1)

Table 2 *Continued*

	Conc. %	nr (test)	Crude % positives	Stand. % positives	95% CI	Minimum % positives	Maximum % positives	Paediatric department crude %
Paraben mix	16	28 569	0.5	0.5	0.4–0.6	0 (several departments)	2.4 (0.6–4.1) Dresden (DE)[D1]	0 (0–1)
Clioquinol	5	11 922	0.3	0.3	0.2–0.4	0 (several departments)	0.9 (0.2–1.6) Barcelona/IMAS (ES)	–
Primin	0.01	16 517	0.2	0.2	0.2–0.3	0 (several departments)	0.9 (0–2) Maribor/Clinic (SI)	–

All allergens in petrolatum, except where indicated otherwise: *water.
TT: extreme prevalence (high or low, respectively) obtained with a TRUE test® allergen.
D1: extreme prevalence (high or low, respectively) obtained with 1-day patch test exposure.
MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDBGN, methyldibromo glutaronitrile (dibromodicyanobutane); ptBFR, *p-tert*-butylphenol formaldehyde resin; IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylene diamine; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

specialized in occupational dermatology, a striking variation in the percentage of patients eventually diagnosed with 'occupational contact dermatitis' has been noted before by Hegewald *et al.*[3] The observation of a lesser proportion of 'occupational contact dermatitis' in a specialized department than in one (albeit small) general department (Trieste vs. Léon; see Table 1) is puzzling. Indeed, varying definitions of work-related skin disease and, in particular, occupational contact dermatitis[22] may be one reason for such diversity, which certainly hampers meaningful international comparisons of all aspects of occupational contact dermatitis and allergy, respectively.[23]

The overall (crude or standardized) prevalence of contact allergies to the EBS allergens are lower for all three metals among the 'general' departments, compared to 2004. Interestingly, the 2009–2012 analysis shows age- and sex-adjusted sensitization frequencies in-between the current and the 2004 results.[5] However, it seems premature to conclude on a downward trend; instead, more detailed analyses seem necessary. These can be combined with exposure assessment, which is greatly aided by the availability of 'spot test' not only for nickel release (the well-known dimethylglyoxime test), but also for cobalt[24] and chromium[25] release. In contrast to metals, the sensitization prevalence for the fragrance screening markers of the EBS, namely fragrance mix I and *Myroxylon pereirae* (balsam of Peru), remained largely unchanged. It should be noted that fragrance mix II and its main allergen hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) had only been introduced to improve the diagnosis of fragrance contact allergy[26] several years after the 2004 data analysis.

Of particular interest are the preservatives, due to the cycles of increasing exposure to a new preservative by broad marketing, increasing awareness of sensitizing potential through case reports, systematic patch testing and awareness of yet another epidemic, and eventual regulation of exposure, either in terms of a ban, or limited use concentrations.[27] Indeed, following the ban of methyldibromo glutaronitrile (MDBGN) in 2004 for leave-on and 2008 for rinse-off cosmetics, the sensitization prevalence observed now is roughly halved. Ongoing exposure by other, non-cosmetic products and new sensitization still occurs.[6] The latest epidemic of contact allergy to preservatives has been observed to MI.[18] The steep increase and the high frequency of MI and MCI/MI contact allergy observed in this study as well as in numerous previous studies from European countries underline the urgency of the regulatory measures to reduce exposure to MI and MCI/MI both in consumers and in an occupational context.[18] The importance of MI is visible in the results presented in terms of sensitization prevalence >7% to the three different test concentrations used – this is extraordinarily high contact allergy prevalence in consecutive patients and has, to the best of our knowledge, not previously been observed for a preservative. Interestingly, the three different patch test concentrations used, i.e. 200, 500 and 2000 ppm (0.2%), all in water

Table 3 Patch test results with the European baseline series[14] obtained in ESSCA departments specialized in occupational dermatology (age- and sex-standardized prevalence). The maximum reading between day (D)3 and D5 (inclusive) was considered. In none of these departments had the TRUE test® been used. If under 'minimum' only one department's name is shown, the results in the columns at the left refer to this department

Haptens	Conc. %	nr (test)	Crude % positives	Stand. % positives	95% CI	Minimum stand. % positives	Maximum stand. % positives
Nickel sulphate	5	2388	19.1	21.7	19.9–23.4	8.6 (5.8–11.4) Osnabrück (DE)	32 (25.8–38.2) Łodz (PL)
Methylisothiazolinone*	0.02	86	4.7	5	0–10.1	Łodz (PL)	–
Methylisothiazolinone*	0.05	535	9	8.2	5.7–10.8	7.5 (4.5–10.6) Osnabrück (DE)	9.3 (4.9–13.8) Heidelberg (DE)
Methylisothiazolinone*	0.2	117	4.3	4.2	0.4–8.1	Łodz (PL)	–
Fragrance mix I	8	2433	6.7	6.4	5.4–7.3	3.7 (1.1–6.3) Helsinki (FI)	9.6 (6.6–12.7) Heidelberg (DE)
MCI/MI*	0.01	2128	5	4.8	3.8–5.7	1.7 (0.7–2.6) Trieste (IT)	9.9 (6.8–12.9) Heidelberg (DE)
MCI/MI*	0.02	229	9.6	10.8	6.4–15.3	Helsinki (FI)	–
Cobalt chloride	1	2451	5.4	6	4.9–7	3.7 (1.2–6.3) Helsinki (FI)	13.9 (9–18.8) Łodz (PL)
Myroxylon pereirae (balsam of Peru)	25	2478	4.8	4.4	3.6–5.2	0.7 (0–2) Cádiz (ES)	6.7 (2.9–10.4) Łodz (PL)
Fragrance mix II	14	1548	3.9	3.6	2.7–4.6	0.8 (0–2.5) łodz (PL)	4.9 (2.9–6.9) Heidelberg (DE)
Potassium dichromate	0.5	2475	3.9	3.8	3–4.6	1.6 (0–3.3) Helsinki (FI)	8.2 (4.2–12.2) Łodz (PL)
p-Phenylenediamine	1	1210	3.8	3.8	2.7–4.8	2.6 (0.6–4.8) Helsinki (FI)	4 (2.6–5.4) Trieste (IT)
Colophonium	20	2484	2.7	2.4	1.8–3	0.7 (0.1–1.3) Trieste (IT)	4.4 (2.2–6.5) Heidelberg (DE)
MDBGN	0.2	1148	3.5	2.8	1.8–3.8	1.2 (0.4–2.1) Osnabrück (DE)	4.8 (2.8–6.8) Heidelberg (DE)
MDBGN	0.3	230	0.4	0.6	0–1.9	Helsinki (FI)	–
MDBGN	0.5	203	0.5	0.5	0–1.5	Łodz (PL)	–
Lanolin alcohol	30	2366	1.2	1.2	0.8–1.7	0.4 (0–0.7) Trieste (IT)	2.8 (several departments)
Thiuram mix	1	2458	3.1	2.9	2.2–3.6	1 (0–3) Cádiz (ES)	5.1 (3–7.1) Heidelberg (DE)
HICC	5	1353	1.6	1.5	0.8–2.2	0 (0–1.5) łodz (PL)	2.5 (0.7–4.2) Heidelberg (DE)
Formaldehyde*	1	2407	1.8	1.8	1.2–2.3	0 (0–2.5) Łodz (PL)	6.9 (3.4–10.4) Helsinki (FI)
Formaldehyde*	2	83	7.2	7.9	1.4–14.3	Łodz (PL)	–
Neomycin sulphate	20	1334	1.6	1.5	0.8–2.1	0 (0–2.4) Cádiz (ES)	4 (0.9–7) Łodz (PL)
Epoxy resin	1	2354	1.9	1.8	1.2–2.3	0.2 (0–0.6) Trieste (IT)	5.5 (2.4–8.6) Helsinki (FI)
Tixocortol pivalate	0.1	435	1.8	1.9	0.6–3.1	1.3 (0–3) Helsinki (FI)	3.1 (0.5–5.7) Łodz (PL)
Quaternium 15	1	1333	0.8	0.8	0.3–1.3	0.1 (0–0.3) Trieste (IT)	2.5 (0–5) Łodz (PL)
Budesonide	0.01	203	1	0.7	0–1.7	Łodz (PL)	–
Budesonide	0.1	353	0.6	0.7	0–1.6	0 (0–2.4) Cádiz (ES)	1.2 (0–2.8) Helsinki (FI)
Mercapto mix (CBS, MBTS, MOR)	1	2274	0.8	0.8	0.4–1.2	0 (0–1.3) Helsinki (FI)	1.9 (0.4–3.4) Heidelberg (DE)
Mercapto mix (MBT, CBS, MBTS, MOR)	2	203	0	0	0–1.5	Łodz (PL)	–
Mercaptobenzothiazole	2	2483	0.7	0.7	0.4–1	0 (several departments)	1.4 (0.3–2.6) Heidelberg (DE)
Sesquiterpenlactone mix	0.1	324	0	0	0–0.9	0 (several departments)	–
ptBFR	1	1857	0.4	0.4	0.1–0.7	0 (0–0.8) Osnabrück (DE)	1.4 (0–3.4) Łodz (PL)
Benzocaine	5	1102	0.6	0.6	0.1–1.1	0.6 (0–1.1) Trieste (IT)	0.8 (0–2.4) Cádiz (ES)
IPPD	0.1	1474	1.2	1	0.5–1.5	0.8 (0–2.4) Cádiz (ES)	1.2 (0.3–2.1) Osnabrück (DE)
Paraben mix	16	2249	0.4	0.3	0.1–0.6	0 (0–2.4) Cádiz (ES)	0.7 (0–1.7) Łodz (PL)
Clioquinol	5	324	0	0	0–0.9	0 (several departments)	–
Primin	0.01	1334	0.1	0.1	0–0.3	0 (several departments)	0.4 (0–1.1) Łodz (PL)

All allergens in petrolatum, except where indicated otherwise: *water.
maximum '–': tested only in one department (see 'minimum').
MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDBGN, methyldibromo glutaronitrile (dibromodicyanobutane); ptBFR, *p-tert*-butylphenol formaldehyde resin; IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylene diamine; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

(aq.), have a very similar yield of positive patch test reactions. However, a formal comparison of diagnostic performance, ideally employing an independent gold standard such as specific history or use-related verification tests, is not possible based on our data, as different sets of patients had been tested. The same holds true for MCI/MI and formaldehyde, the concentration of which had been increased to 200 ppm aq. and 2% aq., respectively, to enhance diagnostic accuracy. Curiously, the overall

yield is very similar, if perhaps showing a slightly higher percentage of positive reactions for the higher test concentration in case of formaldehyde, but, again, a valid comparison is not possible. It should be mentioned that, according to the ESCD patch test guideline,[1] water-based allergens should be dosed with a micropipette, to avoid overdosing with subsequent irritation or even an increased risk of active sensitization. Although currently there is only low exposure to formaldehyde in cosmetics, technical fluids, paints and lacquers, formaldehyde-releasing preservatives such as imidazolidinyl or diazolidinyl urea, DMDM hydantoin, quaternium 15 (the only one included in the EBS), bronopol (2-bromo-2-nitropropane-1,3-diol) and others contribute to a relevant exposure to free formaldehyde,[6] which makes a reliable diagnosis of formaldehyde contact allergy ever so important. Parabens are a widely used class of preservatives.[28] However, in many cosmetic products, they have been replaced with other preservatives due to alleged 'endocrine-disrupting' properties – such replacement by MI can actually be regarded as one of the driving forces of the MI contact allergy epidemic just discussed. The lower sensitization prevalence in the present material [0.5% (95% CI: 0.4–0.6%) vs. 1.0% (95% CI: 0.8–1.2%) in 2004] is possibly a reflection of such lesser usage of parabens.

Compared to 2004, the standardized sensitization prevalence to primin in Europe dropped considerably from 0.78% (95% CI 0.6–1.0%) to 0.2% (95% CI 0.2–0.3%). This is likely due to the availability of primin-free cultivars of *Primula obconica* H. in Europe since 2000.[29] Concerning primin, no difference in sensitization frequency is seen between departments specialized in occupational dermatology compared to general dermatology departments, neither in 2004 nor in 2013/14. Therefore, sensitization to this plant allergen is probably not often related to occupational exposure. Concerning sesquiterpenlactone mix, the frequency of sensitization did not change, with 0.73% (95% CI 0.5–0.9%) in 2004 and 0.7% (95% CI 0.6–0.8%) in 2013/14, respectively. However, to identify contact allergy to Compositae, additional testing of the Compositae mix or other relevant Compositae extracts is recommended, which provides a higher overall detection of contact allergy to plants of the Compositae family.[30] The sensitization prevalence of colophonium, a resin from conifers, a fragrance allergy marker in a broad sense[31] and also used in adhesives, has remained largely stable.

Several active drug components are part of the EBS. Contact allergy to neomycin sulphate declined significantly from 2.1% (95% CI: 1.8–2.3%) in 2004 to 1.2% (95% CI: 1.1–1.4%), which may reflect an overall declining exposure and sensitization. This had actually been identified in Germany[32] and thus further motivated by the notion of previous exposure to the few neomycin-containing drugs being relatively easy to identify (for history-based aimed testing), the German Contact Dermatitis Group had removed neomycin from its baseline series many years ago. However, in other countries, with more widespread exposure, possibly by 'over-the-counter' (OTC) availability, as in the USA, neomycin sulphate may still be worthwhile to test.[33] Two corticosteroid screening allergens are used in the EBS, namely tixocortol pivalate 0.1% pet. and budesonide 0.01% pet. Both corticosteroids are also frequently tested in a 10-fold higher concentration, and there is an ongoing debate both on how to adequately patch-test these difficult allergens[34] and moreover also on how to classify corticosteroid contact allergy.[35] Clioquinol nowadays does not appear to be an important topical drug contact allergen and does not warrant inclusion in the EBS any longer, for which normally a reaction frequency of above 0.5 or 1% in consecutive patients is considered as inclusion criterion[36] – in case of clioquinol, the upper 95% CI is 0.4% and thus falls short of this conventional threshold. Of note, this low prevalence of sensitization has been stable for at least a decade.[3] Benzocaine is an ester-type local anaesthetic used in a range of topical preparations, some available OTC. Despite this, the reaction prevalence is low in the present results, and even lower than in the previous analysis of 2004 data [0.6% (95% CI: 0.5–0.7%) vs. 1.1% (95% CI: 0.8–1.4%)]. The use of a suitable mix of 'caines', including cinchocaine (syn; dibucaine), as a possible replacement of benzocaine in the EBS should be considered, in particular, as benzocaine as screening marker has been found to miss 70% of contact allergies to local anaesthetics.[37]

The one excipient included in the EBS, beyond preservatives and fragrances already discussed, is lanolin alcohol, showing a stable prevalence of sensitization of around 2%. Lanolin (wool alcohols) contact allergy has been somewhat provocatively called a 'myth' in the past[38] and mild irritant patch test reactions are certainly possible, as with other emulsifiers. However, lanolin alcohol must, nevertheless, be regarded as important allergen to screen with, particularly in leg dermatitis patients. Positive reactions should carefully be evaluated, e.g. involving repeated open application or provocative use testing with lanolin alcohol-containing products, to ascertain clinical relevance of a positive patch test reaction. Recently, it has been pointed out that in children and adolescents with atopic eczema, also the lanolin alcohol derivative Amerchol L101 (which has no own INCI name) commonly caused positive patch test reactions.[39] Therefore, it may be worthwhile to further examine the most suitable patch test preparation.

A number of allergens of the EBS are more or less associated with occupational exposure.[40] Among these, *p*-phenylenediamine (PPD) – evidently also important for hair dye self-users and hairdressers' clients – shows some overall decline [3.2% (95% CI: 3.0–3.4% vs. 4.1% (95% CI: 3.7–4.5%) in 2004]. This may be the first indication of a reduction in use of PPD in oxidative hair dyes witnessed, e.g., in Germany, in terms of a replacement with modified PPD derivatives.[41] Unfortunately, exposure to very high skin doses of PPD is still occurring via so-called temporary henna tattoos, as extensively reviewed in de Groot.[42] Rubber allergens are quite prominent in the EBS, with three mixes and one singular allergen, and sensitization is often, but not always, occupation-related. The present data show some

decline of contact allergy to thiuram mix [1.9% (95% CI: 1.8–2.1%) vs. 2.6% (95% CI: 2.3–2.9%) in 2004], while the other rubber additives remained largely stable. It has to be noted that diagnostic work-up of patients with suspected rubber-related allergic contact dermatitis should not solely rely on these four EBS allergens, because as many as 40% with eventually diagnosed contact allergy to rubber additives will be missed if further rubber additives and mix breakdowns are not additionally tested.[7] An in-depth discussion of adequate patch test diagnosis of rubber contact allergy is found in a recent review.[43] The prevalence of contact allergy to *p-tert* butylphenol formaldehyde resin in consecutive patients halved, compared to 2004, which may be indicative of a reduced importance of this adhesive mainly used in footwear; however, reliable exposure information is, as in many fields, lacking.

In conclusion, the comparison between 2004 and 2013/14 demonstrated the remarkable increase in contact allergy to MI and, related, to MCI/MI. Other allergens, including fragrances and metals, remained largely stable, while a substantial proportion of EBS allergens showed a decreasing trend. However, as the sample of European departments is only partly identical with the 2004 analysis, such downward trend should probably not be interpreted as an indication of a decreasing importance of the respective contact allergens; further in-depth analyses such as Garg *et al.*[44] appear necessary to draw firmer conclusions. Based on the present results, and on previous observations, it is suggested to omit the following allergens from the EBS, or possibly replace them with more suitable test preparations:

- Clioquinol
- Primin
- Benzocaine, to be replaced with a suitable caine mix

Contributors

The following members of the ESSCA network contributed data to this analysis in addition to the authors (ordered by country): Werner Aberer (Graz, AT), Andreas Bircher (Basel, CH), Jürgen Grabbe (Aarau, CH), Ulrike Beiteke (Dortmund, DE), Jochen Brasch (Kiel, DE), Thomas Fuchs (Göttingen, DE), Juan García-Gavín (Vigo, ES), Pedro Mercader (Murcia, ES), Inmaculada Ruiz (León, ES), Juan Fco. Silvestre (Alicante, ES), Andrea Peserico (Padova, IT), Maja Kalac Pandurovic (Maribor/Clinic, SI), Nada Kecelj (Ljubljana/Clinic, SI), Tomaž Lunder (Ljubljana/Univ., SI), Mojca Simončič Godnič (Novo Mesto, SI), Marko Vok (Izola, SI), Philippa Cousen and Helen L. Horne (Middlesbrough, UK), Natalie Stone (Newport, UK).

References

1 Johansen JD, Aalto-Korte K, Agner T *et al.* European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195–221.

2 Diepgen TL, Ofenloch RF, Bruze M *et al.* Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol* 2016; **174**: 319–329.

3 Hegewald J, Uter W, Aberer W *et al.* The European Surveillance System of Contact Allergies (ESSCA): results of patch testing the standard series, 2004. *J Eur Acad Dermatol Venereol* 2008; **22**: 174–181.

4 Frosch PJ, Johansen J, Schuttelaar ML *et al.* Patch test results with fragrance markers of the baseline series – analysis of the European Surveillance System on Contact Allergies (ESSCA) network 2009–2012. *Contact Dermatitis* 2015; **73**: 163–171.

5 Uter W, Larese Filon F, Rui F *et al.* ESSCA results with nickel, cobalt and chromium, 2009–2012. *Contact Dermatitis* 2016; **75**: 117–121.

6 Giménez-Arnau AM, Deza G, Bauer A *et al.* Contact allergy to preservatives: ESSCA* results with the baseline series, 2009–2012. *J Eur Acad Dermatol Venereol* 2017; **31**: 664–671.

7 Uter W, Warburton K, Weisshaar E *et al.* Patch test results with rubber series in the European Surveillance System on Contact Allergies (ESSCA), 2013/14. *Contact Dermatitis* 2016; **75**: 345–352.

8 Warburton KL, Bauer A, Chowdhury MMU *et al.* ESSCA results with the baseline series, 2009–2012: rubber allergens. *Contact Dermatitis* 2015; **73**: 305–312.

9 Uter W, Spiewak R, Cooper SM *et al.* Contact allergy to ingredients of topical medications: results of the European Surveillance System on Contact Allergies (ESSCA), 2009–2012. *Pharmacoepidemiol Drug Saf* 2016; **25**: 1305–1312.

10 Uter W, Arnold R, Wilkinson J *et al.* A multilingual European patch test software concept: WinAlldat/ESSCA. *Contact Dermatitis* 2003; **49**: 270–271.

11 Uter W, Schnuch A, Wilkinson M *et al.* Registries in Clinical Epidemiology: the European Surveillance System on Contact Allergies (ESSCA). *Methods Inf Med* 2016; **55**: 193–199.

12 Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47–56.

13 Gefeller O, Pfahlberg AB, Uter W. What can be learnt from nothing? – A statistical perspective. *Contact Dermatitis* 2013; **69**: 350–354.

14 Bruze M, Engfeldt M, Gonçalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series–on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2013; **69**: 263–270.

15 Uter W. Fragrance mix I: TRUE Test versus pet.-based patch test. *Contact Dermatitis* 2015; **72**: 256–258.

16 Uter W, Schwitulla J, Thyssen JP *et al.* The 'overall yield' with the baseline series – a useful addition to the array of MOAHLFA factors describing departmental characteristics of patch tested patients. *Contact Dermatitis* 2011; **65**: 322–328.

17 Schnuch A, Geier J, Uter W *et al.* National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–209.

18 Anonymous. Methylisothiazolinone, quo vadis? (Editorial). *Contact Dermatitis* 2016; **75**: 263–264.

19 Murad A, Marren P. Prevalence of methylchloroisothiazolinone and methylisothiazolinone contact allergy in facial dermatitis: a single centre Irish study. *J Eur Acad Dermatol Venereol* 2016; **30**: 60–62.

20 Gilissen L, Goossens A. Frequency and trends of contact allergy to and iatrogenic contact dermatitis caused by topical drugs over a 25-year period. *Contact Dermatitis* 2016; **75**: 290–302.

21 Uter W, Gefeller O, Giménez-Arnau A *et al.* Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009–2012. *Contact Dermatitis* 2015; **73**: 82–90.

22 Mahler V, Aalto-Korte K, Alfonso JH *et al.* Occupational skin diseases: actual state analysis of patient management pathways in 28 European countries. *J Eur Acad Dermatol Venereol* 2017; **31**: 12–30.

23 Alfonso JH, Bauer A, Bensefa-Colas L *et al.* Minimum standards on prevention, diagnosis and treatment of occupational and work-related skin diseases in Europe – position paper of the COST Action StanDerm (TD 1206). *J Eur Acad Dermatol Venereol* 2017; **31**: 31–43.

24 Midander K, Julander A, Skare L *et al.* The cobalt spot test–further insights into its performance and use. *Contact Dermatitis* 2013; **69**: 280–287.
25 Bregnbak D, Johansen JD, Jellesen MS *et al.* Chromium(VI) release from leather and metals can be detected with a diphenylcarbazide spot test. *Contact Dermatitis* 2015; **73**: 281–288.
26 Frosch PJ, Pirker C, Rastogi SC *et al.* Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. *Contact Dermatitis* 2005; **52**: 207–215.
27 Dillarstone A. Cosmetic preservatives. *Contact Dermatitis* 1997; **37**: 190.
28 Uter W, Yazar K, Kratz EM *et al.* Coupled exposure to ingredients of cosmetic products: II. Preservatives. *Contact Dermatitis* 2014; **70**: 219–226.
29 Christensen LP, Larsen E. Primin-free *Primula obconica* plants available. *Contact Dermatitis* 2000; **43**: 45–46.
30 Paulsen E, Andersen KE, Hausen BM. An 8-year experience with routine SL mix patch testing supplemented with Compositae mix in Denmark. *Contact Dermatitis* 2001; **45**: 29–35.
31 Uter W, Schmidt E, Lessmann H, Schnuch A. Contact sensitization to tree moss (Evernia furfuracea extract, INCI) is heterogeneous. *Contact Dermatitis* 2012; **67**: 36–41.
32 Menezes de Pádua CA, Schnuch A, Lessmann H *et al.* Contact allergy to neomycin sulfate: results of a multifactorial analysis. *Pharmacoepidemiol Drug Saf* 2005; **14**: 725–733.
33 Zug KA, Pham AK, Belsito DV *et al.* Patch testing in children from 2005 to 2012: results from the North American contact dermatitis group. *Dermatitis* 2014; **25**: 345–355.
34 Chowdhury MM, Statham BN, Sansom JE *et al.* Patch testing for corticosteroid allergy with low and high concentrations of tixocortol pivalate and budesonide. *Contact Dermatitis* 2002; **46**: 311–312.
35 Baeck M, Chemelle JA, Goossens A *et al.* Corticosteroid cross-reactivity: clinical and molecular modelling tools. *Allergy* 2011; **66**: 1367–1374.
36 Bruze M, Conde-Salazar L, Goossens A *et al.* Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999; **41**: 241–250.
37 Brinca A, Cabral R, Gonçalo M. Contact allergy to local anaesthetics-value of patch testing with a caine mix in the baseline series. *Contact Dermatitis* 2013; **68**: 156–162.
38 Kligman AM. The myth of lanolin allergy. *Contact Dermatitis* 1998; **39**: 103–107.
39 Lubbes S, Rustemeyer T, Sillevis Smitt JH *et al.* Contact sensitization in Dutch children and adolescents with and without atopic dermatitis – a retrospective analysis. *Contact Dermatitis* 2017; **76**: 151–159.
40 Pesonen M, Jolanki R, Larese Filon F *et al.* Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe – analyses of the European Surveillance System on Contact Allergy network, 2002–2010. *Contact Dermatitis* 2015; **72**: 154–163.
41 Kirchlechner S, Hübner A, Uter W. Survey of sensitizing components of oxidative hair dyes (retail and professional products) in Germany. *J Dtsch Dermatol Ges* 2016; **14**: 707–715.
42 de Groot AC. Side-effects of henna and semi-permanent 'black henna' tattoos: a full review. *Contact Dermatitis* 2013; **69**: 1–25.
43 Warburton KL, Uter W, Geier J *et al.* Patch testing with rubber series in Europe: a critical review and recommendation. *Contact Dermatitis* 2017; **76**: 195–203.
44 Garg S, Thyssen JP, Uter W *et al.* Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. *Br J Dermatol* 2013; **169**: 854–858.